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MODELING THE BIOLOGICAL ACTIVITY OF 2-ARYL-THIAZOLE DERIVATIVES

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ABSTRACT A QSAR study on a set of biologically active molecules belonging to the class of 2-aryl-thiazole, using topological indices, is reported. The purpose of the study is to find the best regression model for prediction of two biological activities: anti-oxidant and anti-inflammatory ones**.**

Keywords*: QSAR, biological activity, prediction, regression analyses, correlation coefficient.*

INTRODUCTION

Quantitative structure-activity relationship (QSAR) is the process by which chemical structures are quantitatively related with a well defined process, such as biological activity. The identification of the crucial factors involved in the relation structure-property is gained by the comparative analysis of a set of molecules. It is achieved with the help of topological descriptors and regression analysis, included in various algorithms. The topological characterization of the chemical structures allows their classification based on a similarity criterion.

The 14 molecules taken in study show anti-oxidant and anti-inflammatory activity and belong to the class of 2-aryl-thiazole derivatives. Their anti-inflammatory capacity was assessed by evaluating the acute phase bone marrow response, phagocytes' activity and NO synthesis (see below). The antioxidant effect of the tested compounds was assessed by evaluating: the total antioxidant response (TAR), the total oxidant status (TOS) and the index of oxidative stress (OSI) [OSI=(TOS/TAR)x100].

Phagocytic activity was assessed with the *in vitro* phagocytosis test by calculating two parameters: the phagocytic index (PI) (PI% = phagocytes with at least one phagocyted germ from 200 leukocytes counted) and the phagocytic activity (PA) (PA = number of germs phagocyted by 100 leukocytes) [3-8].

In acute inflammation there is a significant increase of NO synthesis due to the expression of iNOS (inducible nitric oxide synthesis). This will raise serum nitrates/nitrites concentration, as side metabolites of nitric oxide.

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In order for a molecule to have anti-oxidant effect TAR should raise or TOS should drop, and if both parameters drop, TAR should drop less, or if both rise, TAR should raise more. In order to have anti-inflammatory effect IF, AF and NO should drop.

The anti-inflammatory activity of the tested compounds was higher than that of Meloxicam, the drug taken as reference.

METHOD

The following procedure was used to find the best relationship between structures and the studied biological properties:

- structures are optimized to find a minimum-energy (stable) configuration (PM3, HYPER CHEM version 7.52);
- an index database is generated by using DRAGON 5.0 software and TOPOCLUJ software;
- an exhaustive search to find the best equations (i.e., with the correlation coefficient (R) higher than 0.90), by STATISTICA 6.0, software;

The molecules were designed by the aid of HYPER CHEM software. Geometry optimization was performed with the molecular mechanics method MM+, of the Polak-Ribiere conjugate gradient, at RMS lower than 0.009.

The topological indices were calculated by DRAGON (1630 indices) and TOPOCLUJ (962 indices) software. From these indices, the ones showing the best correlation coefficient in monovariate regression against the biological activity were selected out.

The statistical analysis was performed with STATISTICA software package, consisting in finding the best mono-, bi- and tri-variate regression equation, which can be further used to predict the biological activity of molecules belonging to the same class of those (2-aryl-thiazole derivatives) present in this study.

RESULTS AND DISCUSSION

Fourteen new 2-aryl-thiazole derivatives were synthesized by condensation between derivatives of 4-[2-(4-methyl-phenyl-thiazole-5-yl)-2-oxo-ethoxy]-benzaldehyde and 2-, 3- or 4-(2-aryl-thiazole-4-ylmethoxy)-benzaldehyde, and different carboxylic acid hydrazides.

For these new structures five parameters were calculated, further used in this study, the goal being to find the best regression equation between chemical structure and biological activity.

Table 1 presents the molecules from our set of study and the calculated parameters.

The meaning of the five parameters illustrated in Table 1, are: IF = phagocytic index (phagocytes with at least one phagocyted germ from 200 leukocytes counted); AF=phagocytic activity (number of germs phagocyted by 100 leukocytes); NO=nitric oxide (NO synthesis was evaluated measuring

nitrates/nitrites concentration); TAR=total antioxidant respons; TOS = total oxidant status. The first tree parameters are determined in case of an inflammatory process and the last two are used for testing antioxidant activity.

Table 1. 2-aryl-thiazole derivatives and their properties

Molecule	Formula	IF	AF	NO	TOS	TAR
5b	$C_{31}H_{26}N_4O_3S_2$	16.57 ±1.51	22.86 ±3.02	577.49 ±96.07	33.54 ±2.97	1.0969 ±0.0026
5c	$C_{31}H_{23}F_3N_4O_3S_2$	22.57 ±2.76	45.71 ±4.23	595.8 ±38.61	31.04 ±3.78	1.097 ±0.004
7b	$C_{29}H_{23}BrN_4O_2S_2$	34.57 ±5.13	55.43 ±3.41	1183.35 ±134.13	27.62 ±2.03	1.0978 ±0.0022
7c	$C_{29}H_{20}BrF_3N_4O_2S_2$	23.43 ±3.95	32.28 ±4.07	1121.64 ±123.65	40.18 ±1.83	1.103 ±0.003
7e	$C_{29}H_{20}BrF_3N_4O_2S_2$	31.14 ±4.74	25.14 ±4.88	558.92 ±72.49	35.77 ±3.3	1.0963 ±0.006
7f	$C_{34}H_{24}BrN_3O_5S$	15.86 ±3.29	16.57 ±2.15	580.35 ±72.28	45.9 ±2.46	1.0979 ±0.0023
7h	$C_{29}H_{23}BrN_4O_2S_2$	29.43 ±4.12	58.71 ±2.21	1031.16 ±146.91	27.27 ±3.52	1.1018 ±0.0029
7i	$C_{29}H_{20}BrF_3N_4O_2S_2$	31 ±3.6	73.28 ±4.5	1228.8 ±120.04	25.92 ±2.64	1.104 ±0.0065
7k	$C_{29}H_{24}N_4O_2S_2$	28.57 ±2.99	42.28 ±4.23	1192.44 ±49.95	28.04 ±3.3	1.0983 ±0.0007
7l	$C_{29}H_{21}F_3N_4O_2S_2$	16.57 ±1.51	28.28 ±1.38	888.45 ±155.09	10.98 ±1.36	1.0882 ±0.002
7m	$C_{34}H_{25}N_3O_5S$	30.86 ±2.54	47.43 ±2.22	662.32 ±142.95	9.82 ±1.1	1.0855 ±0.0047
7o	$C_{29}H_{24}N_4O_2S_2$	27.43 ±5.09	62.28 ±4.53	1152.59 ±79.89	26.66 ±2.83	1.0989 ±0.0014
7p	$C_{29}H_{21}F_3N_4O_2S_2$	16 ±3.51	19.14 ±2.54	1257.04 ±157.09	22.57 ±3.44	1.0952 ±0.001
7r	$C_{34}H_{25}N_3O_5S$	26.28 ±4.82	15.43 ±0.79	1158.25 ±91.61	20.35 ±0.69	1.0992 ±0.0032

We looked for the best regression equation in modeling all the five parameters; the best regression equations are listed in the following.

Property: IF.

Monovariate regression:

$y = 27.02+0.849\times Mor13u$

$R = 0.8489;\ s = 1.14;\ F = 30.94$

Bivariate regression:

$y = 21.70-0.31\times MATS3m+0.725\times Mor13u$

$R = 0.8958;\ s = 2.68;\ F = 22.35$

Trivariate regression:

$y = 30.69-0.58\times MATS3m-1.7\times Mor13v+2.20\times Mor13p$

$R = 0.9481;\ s = 2.73;\ F = 29.64$

Property: NO.

Monovariate regression:

y = 6564.2-0.89×TIC2

R = 0.8940; s = 139.58; F = 47.79

Bivariate regression:

y = -9333.75-0.6×IC3+0.475×X[Sh[CfMax[Charge]]]

R = 0.9389; s = 112.03; F = 40.91

Trivariate regression:

y =-22353.63+0.225×ATS4p-0.68×IC3+0.628×X[Sh[CfMax[Charge]]]

R = 0.9427; s = 113.87; F = 26.61

Property: AF.

Monovariate regression:

y = -14.33+0.77×R7p+

R = 0.7703; s = 12.25; F = 17.51

Bivariate regression:

y = -4.31+0.658×H2u-0.67×PDS8[Sh[D3D]]

R = 0.8829; s = 9.42; F = 19.44

Trivariate regression:

y = 101.94-0.55×E3u-0.54×PDS10[Sh[D3D]]+1.09×R7p+

R = 0.9180; s = 8.35; F = 17.85

Property: TOS.

Monovariate regression:

y = -333.6+0.87×EEig10d

R = 0.8702; s = 5.45; F = 37.44

Bivariate regression:

y = -278.28+0.741×EEig10d-0.23×Mor10v

R = 0.8903; s = 5.26; F = 21.02

Trivariate regression:

y =134.52+0.15×RDF040m-0.4×RDF135u-0.35×WkOp[SzMinSzMax U]

R = 0.9473; s = 7.23; F = 6.03

Property: TAR.

Monovariate regression:

y = 1.22-0.88×GATS2v

R = 0.8818; s = 0.003; F = 41.93

Bivariate regression:

y = 0.96+0.562×EEig10d-0.49×Mor10v

R = 0.9355; s = 0.002; F = 38.59

Trivariate regression:

y = 0.96+0.58×EEig10d+0.566×Mor10v-1.00×Mor10v

R = 0.9550; s = 0.002; F = 34.54

Considering that a biological activity is a multi-conditional response, the models showed a clear correlation between activity and molecular structure, particularly in bi-and tri-variate equations. The study needs to be continued to enlarge the data set for a better statistical significance.

CONCLUSION

The class of 2-aryl-thiazoles is known for various biological activities, the anti-oxidant and anti-inflammatory included. The present article reported the modeling of these two bio-activities by using topological indices. Based on the regression models here presented we can predict the biological activity for molecules belonging to the same class and not included in the regression equation.

This theoretical study stand as a support for further experiments in finding molecules with desired anti-oxidant and anti-inflammatory activity.

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